CONGENITAL HEART DISEASE

Non-invasive assessment of ventricular force–frequency relations in the univentricular circulation by tissue Doppler echocardiography: a novel method of assessing myocardial performance in congenital heart disease

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Objective: To describe the first clinical application of a novel tissue Doppler derived index of contractility, isovolumic acceleration (IVA), in the assessment of the ventricular myocardial force–frequency relation (FFR) in the univentricular heart (UVH).
Design: Prospective study.
Setting: Tertiary referral centre.
Interventions: Non-invasive assessment of the myocardial FFR by tissue Doppler echocardiography during atrial pacing.
Results: IVA was used to measure the FFR of the systemic ventricle in patients with structurally normal hearts and in patients with UVHs. Basal IVA of the normal hearts (mean (SD) 1.9 (0.3) m/s^2) was significantly greater than that of UVHs in patients with a dominant right ventricle (RV) (1.0 (0.3) m/s^2) or left ventricle (LV) (0.8 (0.7) m/s^2; $p < 0.05$ for both). Neither the absolute nor percentage change from basal to peak values of IVA with pacing differed between the three groups. Peak force developed by the normal LV was significantly greater than that of the UVH, dominant LV group but not different from that of the UVH, dominant RV group.
Conclusion: Contractility at basal heart rate is depressed in patients with UVH compared with the normal LV. Analysis of ventricular FFRs exposes further differences in myocardial contractility. There is no evidence that contractile function of the dominant RV is inferior to that of the dominant LV over a physiological range of heart rates.

Abnormalities of systolic[1 2] and diastolic[3 4] systemic left ventricular (LV) function have been observed after the Fontan operation. Whereas the diastolic abnormalities persist and may worsen with time,[5] preoperative systolic dysfunction measured by the end systolic wall stress velocity of circumferential fibres shortening corrected for rate has been shown to normalise at early follow up.[1 6] Our ability to detect intrinsic myocardial disease in these geometrically complex and physiologically abnormal ventricles is limited, however. Indices derived from ejection phase measurements are inherently load dependent and can rarely take account of the effects of important co-related phenomena such as the influence of heart rate. The situation is even more complex when the dominant chamber is the right ventricle (RV).

Improving results of the Norwood procedure for hypoplastic left heart syndrome have meant that increasing numbers of survivors reach completion of the Fontan circulation. Intuitively it might be thought that the systemic morphological RV performs less well than the systemic morphological LV. Data suggest that, although ejection phase indices are at most uniformly lower than those for the LV, contractile performance of the systemic RV is not a limiting factor in the biventricular circulation of post-Mustard patients[7] and is not a risk factor for poor early and mid term outcome after the Fontan procedure.[8 9] Furthermore, data from in vitro studies show that the velocity of shortening and timing of isometric contractile force of RV muscle are superior to those of the LV.[10] Comparison of myocardial performance in systemic LV and RV will, necessarily, be flawed. Isovolumic acceleration (IVA), an index of contractile force that takes account of the changes in heart rate and is relatively independent of changes in load, may offer the most robust non-invasive index of LV[11] and RV[12] contractile function. In this study we examine, for the first time using this method, the myocardial force–frequency relation (FFR) in patients with a univentricular heart (UVH) to compare the relative contractile properties of the systemic LV and RV.

METHODS

Patients

The study protocol was approved by the institution's research ethics board. Informed consent was obtained before enrolment in the study. All patients were studied under general anaesthesia at the time of cardiac catheterisation or surgical repair. Muscle relaxants were routinely used in the operating room and in the majority of patients studied in the catheterisation laboratory. Anaesthesia was maintained with a combination of intravenous fentanyl and inhaled isoflurane or an infusion of propofol. The control group consisted of patients with otherwise structurally normal hearts undergoing electrophysiological studies for re-entrant pathways and were studied after successful ablation. Patients with a UVH were studied at the time of diagnostic cardiac catheterisation or immediately preoperatively in the operating room. Patients with significant systemic to pulmonary collaterals, surgically created systemic to pulmonary shunts, or more than a moderate degree of atrioventricular valve regurgitation were excluded.

Abbreviations: FFR, force–frequency relation; IVA, isovolumic acceleration; IVV, isovolumic contraction; LV, left ventricle; RV, right ventricle; S velocity, ejection phase velocity; TDI, tissue Doppler imaging; UVH, univentricular heart

Echocardiography

Our method has been previously described.[11 12] Briefly, tissue Doppler imaging (TDI) was performed with a System V ultrasound scanner (GE Vingmed, Horten, Norway) and a 5 MHz probe. The heart was imaged from a transthoracic apical four chamber view. Imaging parameters were optimised to yield the highest frame rate possible (> 165 frames/s). Pulse repetition frequency was set at the lowest possible value without aliasing. Colour coded myocardial velocities were recorded from the basal mid-wall immediately below (0.5 cm) the insertion of the mural leaflet of the atrioventricular valve of the dominant ventricle in patients with UVHs and of the LV in patients with structurally normal hearts. Velocities were recorded simultaneously with ECG. A cineloop of at least three consecutive cardiac cycles coinciding with end expiration was stored digitally for offline analysis.

Pacing protocol

Patients undergoing electrophysiological studies were paced through the right atrium with endocardial catheters connected to a pulse generator (Model 5328; Medtronic, Minnesota, USA). Patients with UVHs were paced by the transoesophageal route with a 5 French bipolar catheter (TAPCATH 205, CardioCommand, Inc, Tampa, Florida, USA) connected to a high output pulse generator (Model 2380, Medtronic). The pulse width was set to 10 ms. The optimum depth of insertion was judged from the size of the atrial signal.[13] Echocardiographic measurements were made at the resting non-paced heart rate and during atrial pacing from the resting heart rate plus 5 beats/min up to a maximum of 200 beats/min in increments of 10 beats/min. Studies were stopped if systemic blood pressure decreased by 30% of baseline or atrioventricular block developed.

Data analysis

Echopac software (GE Vingmed) was used to analyse the stored TDI data by our previously described method.[11 12] The sample volume (1 × 1 pixel) was placed in the middle of the myocardium at the basal free wall of the dominant ventricle in patients with UVHs and of the LV free wall in patients with structurally normal hearts. The resulting Doppler spectral was displayed and analysed with commercially available software (Echopac, GE Vingmed). Data points were smoothed with a three point moving average filter. Peak myocardial velocities during isovolumic contraction (IVV) and systolic ejection (s wave), and IVA were measured with electronic calipers. Acceleration was calculated as the difference between baseline and peak velocities divided by their time interval.[11 12] Display of the TDI data within the analysis package was optimised by maximally expanding both axes for each beat to minimise measurement error.

Statistical analysis

Data are expressed as mean (SD). Ages and basal and peak tissue Doppler values were compared by *t* test or one way analysis of variance with post hoc Bonferroni multiple comparison as appropriate. Correlation between these variables was assessed by the Pearson method. Measurements of TDI derived FFR for the different patients groups were compared by mixed linear regression for repeated measures (SAS; SAS Institute Inc, Cary, North Carolina, USA). A probability value of $p < 0.05$ was considered significant.

RESULTS

Patients

Transoesophageal pacing was attempted in 39 patients with UVH and was successful in 37. One patient with aortic and mitral atresia and LV hypoplasia had moderately severe tricuspid incompetence. This patient was excluded from further analysis leaving 36 patients with functionally single ventricles. Table 1 shows the morphological diagnoses of these patients. In total, 13 patients with structurally normal hearts (mean (SD) age 12.4 (4.8) years), 19 with UVH, dominant LV (mean age 6.9 (5.3) years), and 17 with UVH, dominant RV (mean age 4.4 (1.5) years) were successfully studied. While the ages of the LV and RV patients were not significantly different ($p > 0.05$), the normal patient group were significantly older than patients with UVH, dominant RV ($p < 0.001$) and those with UVH, dominant LV ($p < 0.01$). Of the UVH, dominant LV group, 10 had undergone previous Fontan completion compared with five of the UVH, dominant RV group. None of the children with UVH had a significant systemic to pulmonary shunt. All patients were normotensive. Of the patients with UVH, eight with dominant RV were receiving ACE inhibitors, whereas six of those with a dominant LV were receiving ACE inhibitors and two were receiving digoxin.

There were no significant correlations between age and either basal ($r = -0.23$, $p = 0.2$) or peak IVA ($r = -0.20$, $p = 0.2$). There were no differences between UVH patients before and after Fontan completion for either basal (1.2 (0.5) *v* 1.1 (0.6), respectively, $p = 0.6$) or peak IVA (4.7 (1.7) *v* 4.9 (1.9), respectively, $p = 0.8$).

Force–frequency relations

Data acquired at rates faster than 170 beats/min were excluded, since we were able to achieve these rates in only a small number of patients due to either atrioventricular block or a significant decrease in blood pressure. Owing to the variability of resting heart rates, a paced rate of 90 beats/min was used as the basal heart rate. IVA (fig 1) measured at basal heart rate was significantly greater in the patients with normal hearts (1.9 90.3) m/s^2) than in the patients with UVH, dominant RV (1.0 (0.3) m/s^2) and with UVH, dominant LV (0.8 (0.7) m/s^2, $p = 0.008$, one way analysis of variance). IVA did not differ significantly at the basal heart rate between the two groups of patients with UVHs. The maximum recorded IVA for the normal hearts, UVH, dominant RV, and UVH, dominant LV were 6.4 (1.3), 4.5 (1.9), and 4.0 (1.9) m/s^2, respectively. Although peak IVA did not differ significantly between the UVH, dominant RV and UVH, dominant LV groups or between the UVH, dominant RV and normal groups, peak force generated by the UVH, dominant LV group was significantly depressed in comparison with the normal group ($p < 0.05$). The optimal heart rate—that is, the rate at which maximum force was achieved—was 160 beats/min in both the normal and the UVH, dominant RV groups. The optimal heart rate of the UVH, dominant LV group could not be determined from these data.

Since age at the time of the study was a significantly dependent variable, this was corrected for by using the logarithm of age in further analysis. There was no significant difference whether patients were studied at the time of cardiac catheterisation or immediately preoperatively. Furthermore, there was no significant difference between whether patients were studied with a Glenn or a completed Fontan circulation. Mixed linear regression for repeated measures of IVA showed that the normal group significantly outperformed the groups of patients with functionally single ventricles ($p = 0.001$). There was a non-significant trend for the UVH, dominant RV group to outperform the UVH, dominant LV group ($p = 0.09$). Neither the absolute nor percentage changes from basal to peak values of IVA ($p = 0.24$ and $p = 0.055$, respectively, one way analysis of variance) (fig 2) with increasing rate of stimulation, however, were significantly different in the three groups.

Table 1 Diagnoses, medications, and ages of patients with univentricular heart (UVH)

	UVH, dominant LV (n = 19)	UVH, dominant RV (n = 17)
Age (years)	6.9 (5.3)	4.4 (1.5)
Diagnosis	Pulmonary atresia, intact septum (3) Double inlet LV, VA discordance (9) Tricuspid atresia, VA concordance (6) Unbalanced AVSD, VA discordance (1)	Mitral atresia with aortic stenosis/atresia (10) Double outlet RV (6) Unbalanced AVSD (2)
Drugs	ACE inhibitor (6) Digoxin (2)	ACE inhibitors (8)

Data are mean (SD) and numbers of patients.
ACE, angiotensin converting enzyme; AVSD, atrioventricular septal defect; LV, left ventricle; RV, right ventricle; VA, ventriculoarterial.

Measurements of changes in IVV (fig 3) with pacing showed a similar relation for the three groups. These rate related changes were not significantly different ($p = 0.14$).

Peak ejection phase velocity (S velocity) at the basal heart rate was 7.8 (2.6), 2.5 (0.8), and 3.2 (1.7) cm/s in the normal LV, UVH, dominant LV, and UVH, dominant RV, respectively. S velocity (fig 4) with pacing was significantly greater in the normal LV group than in patients with UVH ($p < 0.0001$). This difference was clearly observed over the entire range of heart rates studied. S wave velocities for the single RV group were not significantly different from those of the single LV group as heart rate increased ($p = 0.12$).

DISCUSSION

This study shows, for the first time, that ventricular FFRs can be easily measured in patients with congenital heart disease by using IVA derived from TDI recordings during transoesophageal pacing. Basal and heart rate related changes in performance of single ventricles was significantly depressed compared with the normal LV. In patients with UVH, there was no evidence that systemic RV function was differentially depressed.

Non-invasive assessment of RV contractile performance remains difficult and is further complicated in the UVH, where abnormal cavity geometry may invalidate some of the commonly used indices of function. Use of echocardiographic indices such as dP/dt_{max}, from Doppler measurements of regurgitation through atrioventricular valves or the myocardial performance index, may be less dependent on geometry but are significantly affected by changes in preload[14 15] and unable to measure the FFR.[16] Indeed, since the relative change in contractile indices over a range of physiological heart rates is non-linear in both normal and disease states, it may not be appropriate to ignore or "correct" such indices for heart rate. The recently validated tissue Doppler index IVA has been shown to be as sensitive as dP/dt_{max} in detecting contractile change, is relatively independent of loading conditions within a physiological range, and can measure the FFR.[11 12] This is important, as the ability to measure the FFR may allow tailoring of treatment by modifying contractility through control of heart rate. Indeed, this is considered to be one mechanism underlying the beneficial effects of β blockade in patients with heart failure, for example.[17]

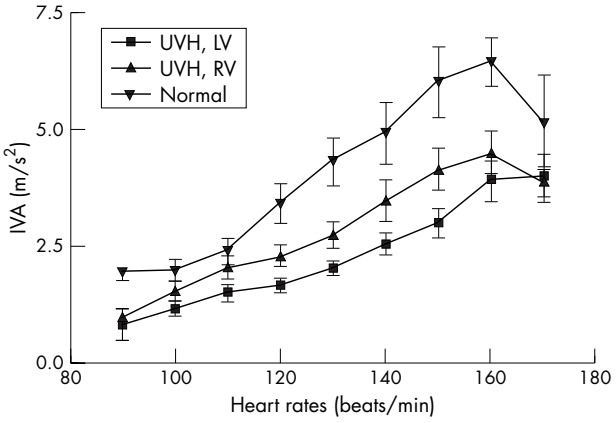

Figure 1 Myocardial force–frequency relations measured in terms of the tissue Doppler derived index isovolumic acceleration (IVA) for functionally univentricular hearts with dominant left (LV) and right (RV) ventricles and structurally normal hearts. Error bars represent SEM.

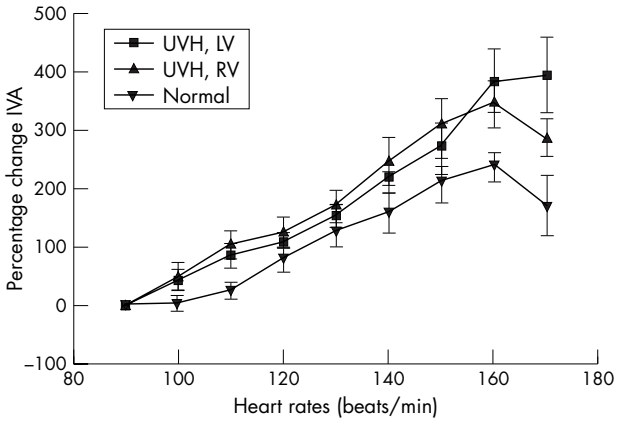

Figure 2 Percentage change in IVA from basal value for each of the three groups studied. Error bars represent SEM.

Force–frequency relation

The FFR, a fundamental property of the myocardium to alter contractile force with changes in heart rate, was first

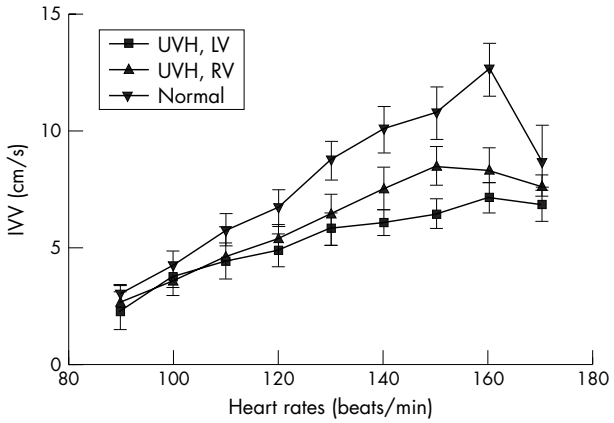

Figure 3 Rate related changes in isovolumic velocity (IVV) for the three groups studied. Error bars represent SEM.

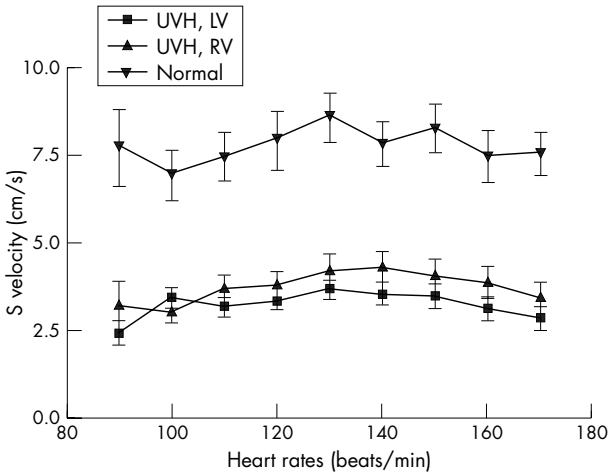

Figure 4 Rate related changes in peak ejection phase velocity (S velocity) for the three study groups. Error bars represent SEM.

described over a century ago.[18] Most evidence points to alterations in the rate of calcium cycling within the myocyte with changes in stimulation frequency being the underlying mechanism.[19–21] As a result of abnormalities in this process caused by disease states, such as dilated cardiomyopathy, for example, reductions in maximum force generated, slope of the FFR, and optimal stimulation frequency have been observed in isolated muscle preparations[22] and clinically[23] through invasive measurements of dP/dt_{max}. This physiological property is therefore important in the assessment of ventricular contractile function but to date has required cardiac catheterisation or in vitro measurements. Indeed, in the only other study of FFR in patients with UVH,[24] similar impairment of FFR was noted during invasive measurements of dP/dt_{max} obtained during cardiac catheterisation. The implication noted by the authors of that study was that systolic calcium cycling was abnormal in these patients. However, these data are difficult to interpret, as only eight patients were studied (including three with UVH of RV type) and only post-bidirectional Glenn, pre-Fontan patients were studied. We studied 36 patients with UVH and so were able to compare groups according to ventricular morphology as well as operative subtype. In this study the assessment of changes in tissue Doppler indices with transoesophageal atrial pacing showed that contractility changed appropriately with increasing heart rate in controls and in patients, albeit with differing rate–contractility trajectories. It was also possible to measure the optimal heart rate—that is, the rate at which contractility was maximal in patients with normal hearts and in those with a systemic RV. IVA was significantly lower in patients than in controls at a basal heart rate of 90 beats/min, and the curves separated further with faster rates. Peak contractile force developed by the normal LV was superior to that of the LV in the UVH circulation but not to that of the UVH RV group, emphasising the importance of measuring the FFR in the assessment of contractile performance and reserve. There was, however, no difference in either absolute or percentage change in IVA between the UVH groups and the normal LV. IVV measured over the same range of heart rates, however, did not differ significantly between the three patient groups. This is probably due to the greater preload dependency of IVV than of IVA.[11]

IVA and S velocity of the single RV and single LV over the range of heart rates studied were not significantly different. Although this finding was initially surprising, RV muscle may not be disadvantaged in comparison with LV muscle. Indeed, over nearly all loading conditions, isolated RV muscle has been shown to shorten faster and have a shorter time to attain peak total tension than LV muscle.[10] Furthermore, ventricular myocardium from patients with pressure loaded RV in association with cyanosis has higher amounts of embryonic or atrial myosin light chain 1,[25] which is also associated with faster maximum velocity of unloaded shortening.[26] While we cannot make inferences from the current study about the amounts of embryonic or atrial myosin light chain, it is interesting to speculate that measurement of IVA, which because of its timing is essentially a measure of ''unloaded'' myocardial contractile properties,[11] may provide added insights into myocardial performance in congenital heart diseases.

Comparison of S velocity in normal LV versus UVH

S velocity for the UVH groups was significantly depressed in comparison with the normal controls. S velocity has previously been shown to correlate well with ejection fraction but is prone to the same limitations in terms of load dependency.[11 12 27] Although it has not been previously seen in patients with univentricular physiology, the finding of significant S velocity depression is perhaps not unexpected. A study of adult patients who had undergone the Fontan operation showed significantly depressed ejection fraction by radionuclide scanning.[28] Furthermore, it has recently been shown that ventricular afterload is significantly greater in patients with the Fontan circulation than in patients with a normal biventricular circulation.[29] This is an important consideration when interpreting measurements of S velocity, since it is affected by changes in afterload, as are all ejection phase indices.

Published data show that the S velocity of the LV lateral wall in an apical four chamber view increases gradually with age.[30] Although study participants with normal hearts were significantly older, the two UVH groups were of comparable age. There are, however, few data regarding changes in S velocities for the RV. A study of 160 normal children (mean age 10.8 years, range 4.0–17.9 years) found median peak S velocity of the basal RV free wall of 12.8 cm/s with 5th–95th centiles lying between 10.7 and 16.5 cm/s.[31] It is likely, therefore, that S velocity in the UVH, dominant RV group (3.2 (1.7) cm/s) and the UVH, dominant LV group (2.5 (0.8) cm/s) was significantly reduced in comparison with normal hearts (7.8 (2.6) cm/s). The difference in age and, probably more important, the difference in afterload must, however, be considered.

Although S velocities increased with increasing heart rate, the magnitude of change was not as great as that for IVA nor IVV. The optimal heart rate was also lower when assessed by S velocity. The greater dependence of S velocities on preload is the likely explanation for this observation.

Study limitations

It was not possible to assess diastolic ventricular function with our protocol. The decremental conduction properties of the atrioventricular node in our patients studied under general anaesthesia resulted in a lengthening of the diastolic period with faster heart rates. Measurement of a ''force–relaxation'' curve was not possible in the majority of patients. This variation in diastolic filling further emphasises the need for a load independent index of contractility when attempting to measure the FFR in patients, clearly seen when comparing the curves generated by changes in S velocity and IVA. Validation of this technique by correlation with invasive measures of contractile function such as dP/dt_{max} would be complicated by the same problem of preload dependence, and indeed may be even more affected in the Fontan circulation due to the recognised increased dependence on preload in these patients.

We were unable to assess the contractile properties of the UVH, dominant LV at rates faster than 170 beats/min. The pacing protocol was stopped due to either atrioventricular block or a significant fall in blood pressure, leaving only a small number of patients with data at faster heart rates. It appears, however, that the optimal heart rate was not reached in the group of patients studied and it is possible that the absolute maximum force generated by the UVH, dominant LV may exceed that of the UVH, dominant RV. This does not, however, detract from the observation that in patients with UVH over the range of heart rates studied, the dominant RV, compared with the dominant LV, performed at a level more closely aligned with that of the LV of normal controls.

Previous studies have shown incoordinate contraction in this group of patients and we cannot assume that measurement of IVA at a single point in the UVH represents global function in the presence of incoordinate contraction. However, a recent study comparing long axis function assessed by echocardiography in adults patients with incoordination after myocardial infarction showed a significant correlation with ejection fraction.[32]

Lastly, our findings of altered contractile properties and differences in FFR should only be interpreted in the context of myocardial performance, not necessarily global circulatory performance. Indeed haemodynamic influences, such as diastolic,[3–5] pulmonary vascular resistance,[33] and ventriculovascular coupling,[29] all contribute to basal and rate related changes in cardiac output. That is not to say, however, that knowledge of FFRs under these circumstances is not a valuable addition to our understanding of this complex haemodynamic milieu.

Conclusions

Ventricular FFR obtained by transoesophageal atrial pacing and tissue Doppler echocardiography is easily measured non-invasively even in patients with complex congenital heart disease. These novel data show that the contractile force at baseline is depressed in patients with UVH relative to the normal LV. Contractile reserve of the systemic RV, however, is no different from that of the LV.

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